

## Golden Berry (*Physalis peruviana*) Juice for Reduction of Blood Glucose and Amelioration of Insulin Resistance in Diabetic Rats

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### ABSTRACT

The study aimed to gather evidence on the potential of golden berry (GB) juice in improving blood glucose level, insulin level, and insulin resistance in type-2 diabetes mellitus (T2DM) in comparison to quercetin supplement in animal model. This study used true experimental pre-post-test study with control group design. Twenty five Wistar male rats were divided into five groups: healthy group (K-), T2DM positive control group (K+), T2DM group with 1 ml/200 g BW/day of GB juice (X1), T2DM group with 5 ml/200 g BW/day of GB juice (X2), and T2DM group with 6 mg/200 g BW/day of quercetin (X3). The T2DM rats were obtained from healthy rats induced by high-fat feed and Streptozotocin (STZ). The result showed that various dosages of GB juice (X1 and X2) were able to lower blood glucose level (-79.15; -110.44; -108.20) and HOMA-IR (-2.40; -2.92; -3.02). In addition, it was also able to increase insulin level (0.26; 1.99; 1.42) compared to (K+) group ( $p < 0.05$ ). In conclusion, GB juice was able to lower blood glucose level, insulin resistance, and increase insulin level in T2DM rats. The GB juice dosage of 1 ml/200 g BW/day and 5 ml/200 g BW/day were better in lowering the blood glucose level and improving insulin resistance compared to quercetin supplement.

**Keywords:** blood glucose, golden berry juice, insulin resistance, type-2 diabetes mellitus

### INTRODUCTION

Type-2 diabetes mellitus (T2DM) is a metabolic disorder marked by elevated blood sugar levels (hyperglycemia) due to decrease in pancreatic  $\beta$ -cell function or insulin resistance (Kahn *et al.* 2014). Type-2 diabetes mellitus, is a global pandemic. International Diabetes Federation (IDF) stated that in 2017, globally there was 425 million cases of T2DM and has been expected to reach 629 million cases in 2045. In Indonesia alone, the number of T2DM was 10 million cases in 2015 (International Diabetes Federation 2017).

One of the underlying pathophysiology of T2DM is insulin resistance (Kahn *et al.* 2014), it is a complex metabolic disorder where the tissue capabilities to use insulin is reduced. Continuous high intake of calories and accumulation of free fatty acids in some tissues can lead to insulin resistance, which perturb the utilization

of glucose in the tissues (liver, muscle, and fat tissue). The insulin resistance causes reduction of insulin interaction with tissues and further disrupts the metabolic pathways of glucose, fat, and protein (Sah *et al.* 2016).

The hyperglycemia in type-2 diabetes mellitus increases the formation of advanced glycation end products (AGEs) and glucose oxidation which produce reactive oxygen species (ROS). The presence of ROS further plays a role in  $\beta$ -cell damage and reduces insulin sensitivity (Qatanani & Lazar 2007). The imbalance of free radicals and antioxidants in the body causes oxidative stress in T2DM (Chikezie *et al.* 2015). Many studies have found that flavonoid content in food has a major role as antioxidant to improve T2DM (Anhe *et al.* 2013). The golden berry (*Physalis peruviana*) is one of such food that is also commonly utilized in Indonesia. The phenolic content in golden berry was 50–250 mg/100 g of fruit and its antioxidant activity was 210.82  $\mu$ moltrolox/100 g of fruit (Puente *et al.*

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2011). Research also shown that golden berry has a role as anti-inflammatory, antioxidant, and anti-diabetic (Sathyadevi *et al.* 2014; Puente *et al.* 2011). The main phenolic compounds in GB fruit are quercetin, myrecetin, and kaempferol (Puente *et al.* 2011).

Fruit juice is considered as functional food because it still contain the micronutrients or active substances from fresh fruits that provides physiological advantages (Ramadan & Moersel 2006). Hassan & Ghoneim (2013) stated that the administration of GB juice with a 1 ml/200 g BW/day dose in diabetic rats, could lower blood sugar significantly compared to untreated diabetic group. Quercetin content on golden berry extract in this study was able to improve pancreas  $\beta$ -cells function as an antioxidant agent. In recent years, quercetin was not only available in food form but also in supplementation and generally introduced as therapy for bacterial infections, gout, hypertension, diabetes mellitus, asthma, and many more (Larson *et al.* 2012). Despite the ease of use of supplement, some patient prefer natural fresh remedies such as the golden berry fruit juice for long term use. Therefore, this study aimed to find evidences on the potential of the golden berry juice compared to quercetin supplement in improving blood glucose level, insulin level, and insulin resistance in type-2 diabetes mellitus rats. The results is expected to contribute to further study for Golden Berry functional food product development and efficacy testing in human subject.

## METHODS

### Design, location, and time

The study used true experimental study with completely randomized design pre-post-test with control group design. This study was conducted at the Integrated Laboratory of Diponegoro University, Semarang for testing the content of quercetin in golden berry juice. Animal care and testing were conducted at Center for Food and Nutrition Research Laboratory, Gadjah Mada University, Yogyakarta from December 2017 to February 2018.

### Sampling

Determination of sample size in this study was based on World Health Organization (WHO 2000) minimum sample for animal assay, which

is 5 rats for each treatment group (WHO 2000). Twenty five male Wistar aged 8–12 weeks with 150–200 g of body weight were obtained from Center for Food and Nutrition Research Laboratory, Gadjah Mada University, Yogyakarta. GB fruits were obtained from the garden in Ciwidey, Bandung regency. Quercetin was obtained from Sigma Aldrich (Q4951, St.Louis, USA), Streptozotocin (STZ) was obtained from Nacalai Tesque Japan and Nicotinamide (NA) was obtained from Nacalai Tesque, Japan. This study also used blood glucose check reagent (Dyasis) and insulin ELISA kit (Fine Test).

The standard rat feed was consisted of Confeed AD II (composition: 12% water, 15% crude protein, 3–7% crude lipid, 6% crude fiber, 7% ash, 0.9–1.1% calcium, and 0.6–0.9% phosphorus) and the high-fat feed (composition: 80% standard feed, 20% lard, and 1% extra cholesterol) were obtained from Center for Food and Nutrition Research Laboratory, Gadjah Mada University, Yogyakarta. Tools for animal care like cages, feeding plate, drinking bottle, digital scales, and blood sampling tools used micro hematocrit and syringe probe.

GB juices were made using basins, blender, cheese cloth, spoon, and measuring cup. Blood analysis used a blood glucose check and insulin ELISA kit. Tools and materials used for testing the content of quercetin in GB juice were 70% methanol, distilled water, Erlenmeyer tubes, beaker glasses, pipettes, ultrasonic (Branson), Whatman paper, micropipette 1,000  $\mu$ L and 10–100  $\mu$ L, test tubes, and High Performance Liquid Chromatography (HPLC) (Shimadzu, Japan).

### Procedures

**Testing for Quercetin content in golden berry juice.** Five ml of the sample juice were mixed with 25 ml of 70% methanol and extracted using the ultrasonic at 30°C for 20 minutes. Extracted sample was stored in freezing temperature for 24 hours and then filtered through a 0.45  $\mu$ m filter. A 20 ml of sample was induced to HPLC instrument. The HPLC analysis was performed using a Shimadzu-LC system equipped with a UV-Vis detector (SPD-20AV), a column Purospher® STAR C18 (250 mm x 4.0 mm, 5  $\mu$ m), a flow rate of 1.1 ml/minutes, a column temperature of 30°C, a mobile phase of Methanol : Acetonitrile : Water (60:20:20) % v/v and a detection wavelenght of 254 nm.

### Conditioning of type-2 diabetes mellitus.

Twenty-five Wistar male rats were acclimatized to individual cages for 7 days given the standard feed and water. The room temperature ranged 25–28°C with 12 hours light cycle (6:00 a.m. to 6:00 p.m.). Rat's cages was cleaned every day. Blood sampling was conducted through plexus retroorbitalis to standardize blood glucose before it was conditioned with type-2 diabetes mellitus. Twenty rats were conditioned T2DM with high-fat feeding for 14 days (Sathyadevi *et al.* 2014) followed by NA induction with the dose of 110 mg/kg body weight via the intraperitoneal injection and 15 minutes later were given the STZ intraperitoneal induction with a dose of 45 mg/kg body weight (Ghasemi *et al.* 2014). Before the STZ induction, rats were fasted for 8–10 hours. After 3 days of STZ induction, rats were fasted for 8–10 hours (Gheibi *et al.* 2017) and 2 ml blood drawn through the plexus retroorbitalis for blood glucose and insulin levels analysis. Rats full filed the T2DM criteria if the fasting serum glucose levels was  $\geq 200$  mg/dl (Gheibi *et al.* 2017).

**Treatments of golden berry juice and quercetin.** Rats were divided into 5 groups: healthy group without treatments (K-), T2DM positive control group without treatments (K+), T2DM group with treatment of 1 ml/200 g BW/day of GB juice (X1), T2DM group with treatment of 5 ml/200 g BW/day of GB juice (X2), and T2DM group with treatment of 6 mg/200 g BW/day of quercetin (X3). The dose of 1 ml/200 g BW/day of GB juice was based on Hassan & Ghoneim (2013) who stated that the dose could lower blood glucose in diabetic rats significantly, while the 5 ml/200 g BW/day dose of GB juice was based on  $\pm 1$  glass of fruit juice consumed by humans. Quercetin was used as standard therapy in experimental animals with T2DM. The 6 mg/200 g BW/day dose of GB juice was the effective dose to lower blood glucose significantly compared to T2DM control group based on previous study of Chis *et al.* (2015).

Quercetin was homogenized with a 0.5% Sodium-Carboxymethyl cellulose (NA-CMC) each into 5 ml of volume. The making of GB juices and quercetin solution were prepared every day in the morning then immediately administered to T2DM rats via a gastric tube once a day. The GB juice and quercetin in T2DM rats were administered for 28 days. Blood sampling was conducted at the end of the study through

plexus retroorbitalis for analysis of blood glucose and insulin levels. Insulin resistance level was indicated by the value of Homeostasis Model Assessment Insulin Resistance (HOMA-IR) with the formula as follow;  $HOMA-IR = (\text{blood glucose level (mg/dl)} \times \text{insulin level } (\mu\text{U/ml})) \div 405$  (Esteghamati A *et al.* 2010). The study methods had received approval from the Ethics Committee for Health Research in Diponegoro University and Dr. Kariadi Hospital, register number 89/EC/H/FK-RSDK/XII/2017.

### Data analysis

Data normality was tested by Shapiro-Wilk test. All of the data had normal distributions, thus the testing for the differences between before and after treatments used the paired t-test. Analysis of the effects of the differences between groups used the One-Way ANOVA test followed Tamhane post hoc ( $p < 0.05$ ) for blood glucose and HOMA-IR analysis, while for insulin analysis it was followed by Bonferroni post hoc test ( $p < 0.05$ ).

## RESULTS AND DISCUSSION

The quercetin content in GB juices and fruit form have been reported previously (Puente *et al.* 2011). The quercetin's content of GB juice in this study was 20.775  $\mu\text{g/ml}$  of juice.

**Conditioning of type-2 diabetes mellitus.** Prior to the treatment of GB juice and quercetin, blood glucose level was tested as a standard category of healthy rats and showed the homogeneous level of blood glucose level in the samples (Table 1). Conditioning of type-2 diabetes mellitus in this study was conducted by high-fat feeding for 14 days and induction of STZ. Blood glucose levels of all rats were more than 200 mg/dl after conditioning of T2DM (Table 2).

High-fat feeding aimed to establish condition of insulin resistance. It led to reduction in the activation of phosphatidylinositol 3-kinase (PI3K)/Akt, which affected tyrosine phosphorylation and decreased IRS so it could reduce insulin signaling (Gheibi *et al.* 2017). The STZ induced later causes a breakdown of deoxyribonucleic acid strand (DNA) and overexpression activation of poly synthase (ADP-ribose) which was an enzyme to repair DNA. The rats was induced with NA at 15 minutes prior the STZ, it aimed to provide protection for pancreatic

Table 1. The initial glucose level standardization

| Treatment groups | Initial glucose levels | p     |
|------------------|------------------------|-------|
| K(-)             | 73.94±15.76            | 0.319 |
| K(+)             | 69.26±5.77             |       |
| X1               | 87.46±9.06             |       |
| X2               | 73.27±5.93             |       |
| X3               | 69.26±10.59            |       |

p: One-Way ANOVA test. K(-): healthy group + without treatments, K(+): T2DM + without treatments; X1: T2DM group + GB Juice 1 ml/200 g BW/day (X1); X2: T2DM group + GB Juice 5 ml/200 g BW/day; X3: T2DM group + Quercetin 6 mg/200 g BW/day; n: 25 samples

β-cells from toxic effects of excessive STZ and created type-2 diabetes mellitus in rats (Zuloaga *et al.* 2014)

**The administration of golden berry juice on levels of blood glucose, insulin, and HOMA-IR.** Paired t-test showed that there were a decrease in blood glucose level (Table 2), an increase in insulin level (Table 3), and a decrease in HOMA-IR value (Table 4) with treatment of GB juice with a 1 ml/200 g BW/day dose and 5 ml/200 g BW/day dose significantly in the before and after treatments ( $p < 0.05$ ). There were significant differences in changes of mean value with GB juice X1 and X2 treatments compared to the K(+) in lowering blood glucose level, increasing insulin level, and decreasing HOMA-IR ( $p < 0.05$ ). This findings were in line

with Hassan & Ghoneim (2013) who stated that administration of GB juice 1 ml/day could lower blood glucose significantly compared to diabetic control group and blood glucose level in group with The GB juice treatment was comparable to healthy rats group. Further, Sathyadevi *et al.* (2014) also found that GB extract could lower blood glucose and increase insulin levels significantly compared to diabetic control group.

The decreased values of blood glucose level in treatments of GB juice 1 ml/200 g BW/day and 5 ml/200 g BW/day were equal to quercetin at dose of 6 mg/200 g BW/day. It was no significant differences between treatments in X1, X2, and X3 in the Tamhane post hoc test ( $p > 0.05$ ) (Table 3). The largest decrease in blood glucose level was shown by the GB juice treatment of 5 ml/200 g BW/day with the value of  $110.44 \pm 10.63$ . It was most likely influenced by the rich antioxidants contents of GB juice in addition to its quercetin content. Previous study found that GB juice contains several phenolic substance, including quercetin as major phenolic content and followed by myricetin and kaempferol (Puente *et al.* 2011) which could play a role in decreasing blood glucose level.

As anti-diabetic agents, quercetin, myricetin, and kaempferol available at various tissues, such as in the muscle. Quercetin for example, promotes glucose uptake in the skeletal muscle tissue by increasing the glucose transporter 4 (GLUT4) translocation. In the liver, these agents improve the glucokinase activity to increase glucose storage in the liver through activation of AMP-activated protein kinase (AMPK). AMPK is

Table 2. Blood glucose levels before and after treatments of golden berry juices and quercetin

| Treatment groups | Blood glucose level (mg/dl) |              | $\Delta$                    | p'     | p      |
|------------------|-----------------------------|--------------|-----------------------------|--------|--------|
|                  | Before                      | After        |                             |        |        |
| K(-)             | 82.76±6.17                  | 100.93±4.50  | 18.17±6.16 <sup>a</sup>     | 0.003* | 0.000* |
| K(+)             | 212.93±9.42                 | 282.30±20.75 | 69.37±25.31 <sup>a</sup>    | 0.004* |        |
| X1               | 221.02±9.97                 | 141.87±6.05  | -79.15±12.56 <sup>ab</sup>  | 0.000  |        |
| X2               | 224.16±11.91                | 113.72±4.43  | -110.44±10.63 <sup>ab</sup> | 0.000* |        |
| X3               | 214.05±14.04                | 105.85±2.51  | -108.20±14.12 <sup>a</sup>  | 0.000* |        |

p': Paired t-test; p: One-Way ANOVA test; <sup>a</sup>  $p < 0.05$  Tamhane post hoc test with K(+); <sup>b</sup>  $p < 0.05$  Tamhane post hoc test with X1; no significant differences in X2 and X3; K(-): healthy group + without treatments; K(+): T2DM + without treatments; X1: T2DM group + GB Juice 1 ml/200 g BW/day (X1); X2: T2DM group + GB Juice 5 ml/200 g BW/day; X3: T2DM group + Quercetin 6 mg/200 g BW/day; n: 25 samples



Table 3. Mean values of insulin level before and after treatments of GB juices and quercetin

| Treatment groups | Blood glucose level (mg/dl) |            | $\Delta$                  | p'     | p      |
|------------------|-----------------------------|------------|---------------------------|--------|--------|
|                  | Before                      | After      |                           |        |        |
| K(-)             | 16.49±0.19                  | 15.65±0.22 | -1.09±0.39 <sup>abc</sup> | 0.003* |        |
| K(+)             | 12.72±0.16                  | 11.82±0.14 | -0.90±0.19 <sup>bc</sup>  | 0.000* |        |
| X1               | 12.76±0.12                  | 13.02±0.14 | 0.26±0.11 <sup>ac</sup>   | 0.007* | 0.000* |
| X2               | 12.74±0.26                  | 14.53±0.17 | 1.99±0.30 <sup>ab</sup>   | 0.000* |        |
| X3               | 12.69±0.23                  | 14.12±0.18 | 1.42±0.35 <sup>abc</sup>  | 0.001* |        |

p': Paired t test; p: One-Way ANOVA test; <sup>a</sup> p<0.05 Bonferroni post hoc test with K(+); <sup>b</sup> p<0.05 Bonferroni post hoc test with X1; <sup>c</sup> p<0.05 Bonferroni post hoc test with X2; K(-): healthy group + without treatments; K(+): T2DM + without treatments; X1: T2DM group + GB Juice 1 ml/200 g BW/day (X1); X2: T2DM group + GB Juice 5 ml/200 g BW/day; X3: T2DM group + Quercetin 6 mg/200 g BW/day; n: 25 samples

an enzyme that regulates the homeostatic energy in the body through several mechanisms such as inhibiting the gluconeogenesis, increases the fatty acid oxidation, and increases the expression of GLUT4. In the gut, these agents help to decrease maltase activity and glucose transporter 2 (GLUT2) that can reduce the absorption of glucose in the gut (Anjani *et al.* 2018; Alkhalidy *et al.* 2015).

The decreased insulin levels indicated a functional disorder of pancreatic  $\beta$ -cells and a reduction in pancreatic islet cells because conditioning of type-2 diabetes mellitus by high-fat feeding and induction of STZ. Antony *et al.* (2017) stated that histopathology test of

pancreatic tissue in animal fed by high-fat and STZ induction showed reduction in pancreatic islet cells. This condition could form amyloid which triggered the ROS. The changes in insulin levels were significantly different between X1, X2, and X3 in Bonferroni post hoc test (p<0.05) (Table 4). The highest elevated levels of insulin could be seen in treatment of GB juice of 5 ml/200 g BW/day with a mean value of 1.99±0.30. It was thought because of other active substances contents in addition to quercetin that help protect pancreatic  $\beta$ -cell and worked as an antioxidant agents. Puente *et al.* (2011) stated that GB juice contained vitamin C, vitamin E, quercetin, myricetin, and kaempferol. Those contents

Table 4. Mean values of HOMA-IR before and after treatments of GB juices and quercetin

| Treatment groups | Blood glucose level (mg/dl) |           | $\Delta$                | p'     | p      |
|------------------|-----------------------------|-----------|-------------------------|--------|--------|
|                  | Before                      | After     |                         |        |        |
| K(-)             | 3.42±0.28                   | 3.89±0.13 | 0.48±0.22               | 0.028* |        |
| K(+)             | 6.69±0.29                   | 8.24±0.61 | 1.55±0.82               | 0.027* |        |
| X1               | 6.96±0.33                   | 4.56±0.17 | -2.40±0.39 <sup>a</sup> | 0.000* | 0.000* |
| X2               | 7.06±0.40                   | 4.14±0.19 | -2.92±0.29 <sup>a</sup> | 0.000* |        |
| X3               | 6.71±0.34                   | 3.68±0.09 | -3.02±0.37 <sup>a</sup> | 0.000* |        |

p': Paired t test; p: One-Way ANOVA test; <sup>a</sup> p<0.05 Tamhane post hoc test with K(+); K(-): healthy group without treatments; K(+): T2DM + without treatments; X1: T2DM group + GB Juice 1 ml/200 g BW/day (X1); X2: T2DM group + GB Juice 5 ml/200 g BW/day; X3: T2DM group + Quercetin 6 mg/200 g BW/day; n: 25 samples

can help quercetin in GB juice in providing more protection to  $\beta$ -cells as antioxidant agents. (Garcia-Bailo *et al.* 2011; Al-Numair *et al.* 2015) compared to quercetin alone.

GB juice with a dose of 1 ml/200 g BW/day and 5 ml/200 g BW/day had same effect with a 6 mg/200 g BW/day of quercetin treatment in improving insulin resistance as shown in Tamhane post hoc test with  $p > 0.05$  at X1, X2 and X3 treatments (Table 4). Previous study found that phenolic compounds and antioxidant activity in GB juice was high. Phenolic compound in GB juice provides a great potential for prevention or management of chronic disease.

Our findings supports the Choi *et al.* (2015) findings which stated that administration of quercetin for 10 weeks to rats induced by STZ could lower HOMA-IR significantly compared to diabetic control group (Choi *et al.* 2015). Quercetin is a powerful antioxidant that can capture free radicals and bind transition metal ions. Quercetin is also one of the best ROS ( $O_2^-$  and  $ONOO^-$ ) catcher. Anti-inflammatory effect of quercetin was able to reduce levels of pro-inflammatory cytokines like tumor necrosis factor alpha (TNF- $\alpha$ ) by inhibiting the expression of Nuclear Factor Kappa Beta (NF- $K\beta$ ) (Choi *et al.* 2015; Luo *et al.* 2015). The inhibition of NF- $K\beta$  expression could reduce insulin receptor substrate (IRS)-1 serine phosphorylation and increase expression of IRS-1 (Luo *et al.* 2015). IRS-1 protein was an important protein in improving insulin sensitivity.

## CONCLUSION

We found evidences that GB juice was able to lower blood glucose level, increase insulin level, and improve insulin resistance. The effect of GB juice with a dose of 1 ml and 5 ml is comparable to quercetin with an administration dose of 6 mg/200 g BW/day in improving the blood glucose and HOMA-IR. In addition, the GB juice was better than quercetin in improving the insulin level. This corroborated the findings that GB juice is a potential nutrition support for type-2 diabetes mellitus. Further research is necessary to test the complete phytochemical contents of GB juice and to analyze its effect on other anti-inflammatory and antioxidant parameters in T2DM to deepen our understanding on the role and mechanisms of GB juice in T2DM.

## ACKNOWLEDGEMENT

The author would like to thank to Integrated Laboratory of Diponegoro University, Semarang, Center for Food and Nutrition Research Laboratory, Gadjah Mada University, Yogyakarta, Diponegoro University for access and technical support. The authors have no conflict of interest.

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